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LETTERS AND CORRESPONDENCE

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All-*trans* Retinoic Acid-Induced Multiple Mononeuropathies

To the Editor: All-trans retinoic acid (ATRA) is widely used as a differentiation therapy to induce a complete remission in patients with acute promyelocytic leukemia (APL) [1]. The major adverse effect during ATRA therapy is an increase of leukocytes, which is often accompanied by retinoic acid syndrome [2]. This reaction is characterized by fever, respiratory distress, radiographic pulmonary infiltrates, pleural effusions, and weight gain [3]. It has also been reported that ATRA-associated neurological symptoms such as headache and pseudotumor cerebri [4] are mainly caused by intracranial hypertension. We describe a patient who developed multiple mononeuropathies during ATRA therapy for APL.

A 23-year-old Japanese female was admitted with fever and purpura in November 1997. APL with disseminated intravascular coagulation was diagnosed. She received ATRA (45 mg/m^2/day) with chemotherapy including daunorubicin (40 mg/m^2/day, on days 9, 10, 21, and 22) and behenoyl cytarabine (200 mg/m^2/day, on days 9, 10, 11, 21, 22, and 23), and supportive therapy for disseminated intravascular coagulation. She had a slight headache after administration of ATRA, but there were no findings on the neurological examination and computed tomography scan of the brain. On the seventeenth day after admission, a neurosurgical operation was performed because of acute subdural hematoma. Although ATRA-associated headache persists, no symptoms remained, which were caused by intracranial hemorrhage and operation. Furthermore, she complained of diplopia, and burning pain and contact dysaesthesiae at the dorsum of the left hand and the right foot on day 21 of the ATRA treatment. She also had weakness in the same extremities. Tendon reflexes were normal. Electrophysiologic study revealed a decrease of right peroneal nerve conduction velocity and amplitude. Although right abducens nerve palsy and visual disturbance were present, there were no papilloedema and abnormalities on magnetic resonance imaging of the brain. Lumbar puncture showed normal cerebrospinal fluid with normal pressure. She had no manifestation of autonomic disturbances. ATRA was discontinued because a complete remission was achieved on day 51 after administration of ATRA. Total dosage of ATRA was 3,390 mg. She received three times the intensive postremission chemotherapy (daunorubicin, cytarabine, mitoxantrone, mercaptopurine, and prednisolone). Symptoms of peripheral neuropathy and findings on electrophysiologic study gradually improved as well as headache and dry skin after discontinuation of ATRA, in spite of additional chemotherapy. The right abducens nerve palsy also partially improved.

To the best of our knowledge, this is the first report of ATRA-induced multiple mononeuropathies. Neurological symptoms might be considered as atypical pseudotumor cerebri with focal neurological sign [5]. However, there was no evidence of intracranial hypertension. Furthermore, we carefully excluded a possibility that other medication including anticancer drugs induced peripheral neuropathy. Clinicians should be aware of this potential side effect in patients receiving ATRA.

Satoshi Yamaji
Heiwa Kanamori
Aki Mishima
Shin Fujisawa
Shigeki Motomura
Hiroshi Mohri
The First Department of Internal Medicine, Yokohama City University School of Medicine, Yokohama, Japan

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Soft Drink Abuse, Malnutrition, and Folic Acid Deficiency

To the Editor: Herein, we report a 28-year-old woman who presented with severe macrocytic anemia in November 1996. Her past medical history was unremarkable except for asthma and one episode of acute synovitis a few years earlier. Her blood count was normal two years earlier.

She is a housekeeper who drank alcohol very rarely and used nonsteroidal anti-inflammatory drugs occasionally. She presented with a history of weakness, a 7.5 kg weight loss in the past two months and of nausea, vomiting, and loss of appetite in the last three weeks. Her food intake for this period consisted almost exclusively of the soft drink Coca-Cola. There was no malabsorption symptoms. Physical examination revealed a severe obesity (126 kg, 1.58 m, body mass index over 50). She was slightly icteric and her tongue was reddened and smooth with papillary atrophy. The neurological examination was normal. The first blood count showed a severe anemia with a hemoglobin (Hg) of 51 g/l, a hematocrit of 0.147 L/L (0.37–0.47), a mean corpuscular volume (MCV) of 99.5 fl (normal 82–94), and reticulocytes at 1.8%. Leukocytes were reduced to 3.3×10^9 g/l (normal 150–450).

Blood smear revealed a marked anisocytosis, no ovalocytosis, quite a few dacryocytes, polychromatophilia, and erythroblasts. A discrete myelemia with a left shift was noted; there were no hypersegmented neutro-

phils. The biochemical analysis was remarkable only for an elevated lactate dehydrogenase level (3,198 U/l) and bilirubin (52 μmol/l). Serum levels of proteins and albumin were normal as was the iron status. However, serum level of folic acid showed a severe deficiency with values below 1.3 nmol/l (normal above 3.5, deficiency below 2.5). Serum level of vitamin B12 was 100 pmol/l (normal above 150, deficiency below 100). Intrinsic factor antibody was negative.

A malabsorption evaluation was performed, including duodenal biopsies, and was noncontributory. A bone marrow aspiration was performed and was compatible with megaloblastic anemia; there was a marked erythroid dysplasia, a few giant metamyelocytes, and the myeloid on erythroid ratio fell to 1.5:1. Alkaline phosphatase of leukocytes score was elevated (212, normal 20–80). Haptoglobin was undetectable and direct Coombs' test was negative. Hepatic function tests, including viral serologies were normal, as were the thyroid function tests. The sucrose hemolysis test and Ham's acid hemolysis test were negative.

A careful review of the patient's dietary habits showed poor nutrition, consisting mostly of bread, rice, potatoes, liver, and a great amount of dairy products. She regularly ate snacks consisting of candies, ice cream, and potato chips. However, what was most remarkable was the consumption of approximately three liters of Coca-Cola per day. This soft drink does not contain any folic acid and has no known folic acid inhibitor. Dietary evaluation showed an energetic intake of 1,500 kcal per day, 40 mg of proteins per day, and 70 mg per day of folic acid (normal is 185 mg per day). The patient received one transfusion of packed red cells, 1,000 mg of B12 vitamins and folic acid, 5 mg IV for one dose, then 5 mg po die for four days, 10 mg po die for two days, 15 mg po die for two months followed by 5 mg po die for two months. Then it was stopped. She also received nutritional counseling.

The patient improved rapidly with disappearance of her symptoms of weakness and vomiting. Ten days after beginning her treatment, her blood count showed a Hb increase from 51 to 79 g/l, and an MCV of 97 fl; reticulocytes were increased at 18%. Platelets were still at 141×10^9 g/l but leukocytes were normal. Seventeen days later, Hb was 105 g/l and platelets were normal.

After one year of follow-up, her blood count remains normal; serum levels of folic acid and vitamin B12 are normal. She is taking neither folic acid nor B12 vitamin supplements. Her diet has improved but remains deficient.

This case is one of severe macrocytic anemia due to a severe deficit in folic acid. This is the first case to our knowledge in which excessive consumption of soft drinks combined with malnutrition is reported as the main cause of folic acid deficiency. This deficiency has been reported so far mainly in a population of alcoholics and substance abusers. The underlying mechanism has not been elucidated.

It is interesting to note that this patient was severely obese, suggesting that malnutrition must not be overlooked, even in this population; intake of vitamins and elements is expected to be sufficient but quality of intake may cause a significant deficiency in one or more of these.

Finally, it is a reminder that nutrition status must be well assessed and that counseling is crucial.

Guylaine Gaudet
Fellow in Hematology, Hôpital du Sacré-Cœur de Montréal, Affiliated Hospital, University of Montreal, Canada

Jacques Laplante
Hemato-Oncologist, Hôpital du Sacré-Cœur de Montréal, Affiliated Hospital, University of Montreal, Canada

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Sex Difference in Myeloperoxidase Activity of Neutrophils

To the Editor: Activated neutrophils produce several antimicrobial oxygen metabolites, including superoxide anion, hydrogen peroxide, hydroxyl radicals, hypochlorous acid, and single oxygen [1]. These reactive metabolites are generated by a reduced nicotinamide adenine dinucleotide phosphate (NADPH)-dependent oxidase, located on the plasma membrane, and a myeloperoxidase (MPO), located in the lysosome [2]. The former three metabolites are produced even in MPO deficiency, so it may be difficult to consider that MPO deficiency is one of the causes for clinically significant failure of neutrophil function. However, in some patients with MPO deficiency, the cytotoxic activities against bacteria and fungi are decreased in neutrophils [3,4]. Therefore, measurement of MPO activity in neutrophils may be useful for evaluating a part of the defense mechanism. Recently, an automated hematology system, which differentiates white blood cells, has come into widespread use. With this system, MPO activity, which represents the MPO staining intensity, is measured as the mean myeloperoxidase index (MPXI) of neutrophils. In this study, therefore, we examined MPO activities of neutrophils in normal subjects.

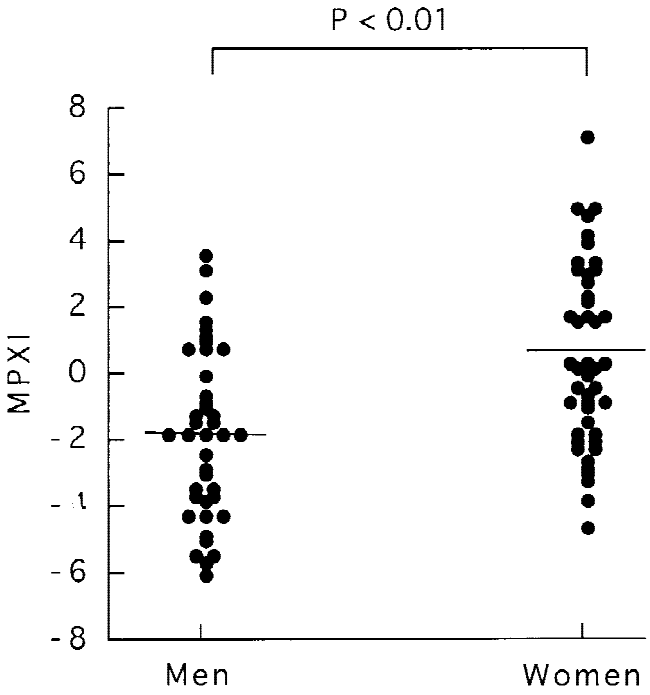

Fig. 1. The mean MPXI of neutrophils in normal men and women.

The subjects studied were 41 normal men (mean age, 36 years; range, 19–57 years), and 46 normal women (mean age, 32 years; range, 21–47 years). The MPXI of peripheral blood was measured using the automated hematological analyzer THMS-H2 (Bayer Technicon, Tarrytown, NY). We found that the MPXI in normal women ($n = 46$, 0.3 ± 2.7, mean ± SD, $P < 0.01$) was significantly higher than that in normal men ($n = 41$, -1.8 ± 2.4) (Fig. 1). This sex difference suggests that some microbicidal activity may be stronger in women than in men. In support of this finding, it was reported in mass surveys that the infection rate of women was lower than that in men in the tinea of dermatophytic infection [5]. Furthermore, this suggests that sex steroid hormones may affect MPO activity, that is the MPXI. Indeed, we found that the change of the MPXI in a woman synchronized with that of basal body temperature and that of serum concentration of estradiol with some phase shift, during three menstrual cycles. However, the MPXI in a man did not change during the 12 weeks of measurement. Also, the results of nitro blue tetrazolium (NBT) reduction and neutrophil number did not change during this period in both subjects. To study the direct effect of sex hormone on the MPO activity, we exam-

ined the changes of MPXI 2 and 3 hr after the addition of estrone (5,000 pg/mL), B-estradiol (5,000 pg/mL), estriol (5,000 pg/mL), or testosterone (100 ng/mL) to peripheral blood in vitro, but we found no effect.

Taken together, these data indicate that: 1. the MPXI of neutrophils, which is measured easily by an automated hematological analyzer and represents MPO activity, is higher in women than in men: 2. the menstrual cycle affects the MPXI; and 3. the MPXI may be useful as a partial index for microbicidal activity of neutrophils.

Osamu Kabutomori
Takehiko Yanagihara
The Central Laboratory for Clinical Investigation, Osaka University Hospital, Osaka, Japan

Yoshinori Iwatani
Department of Clinical Laboratory Science, Faculty of Medicine, Osaka University, Osaka, Japan

Atsushi Kawarazaki
Miwako Kabutomori
Kawarazaki Hospital, Osaka, Japan

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Case of Hepatosplenic γδ T-Cell Lymphoma Presenting With Severe Hypersplenism

To the Editor: Pancytopenia with severe neutropenia at presentation is a rare finding in hepatosplenic γδ T-cell lymphoma (TCL) [1–4].

In March 1997, an 18-year-old male was hospitalized with fever, abdominal discomfort, and fatigue. Despite the absence of either superficial or profound lymphadenopathies as confirmed by a computerized tomographic scan of the chest, abdomen and pelvis, hepatomegaly with massive splenomegaly, 3 and 23 cm below the costal margins, respectively, were noted. The peripheral blood count showed pancytopenia and severe neutropenia (Hb 6.3 g/dl, Hct 20%, platelets 20×10^9/l,leukocytes 2×10^9/l, neutrophils 0.68×10^9/l). No abnormal cells were detected in the peripheral blood and in the bone marrow (aspirate and biopsy). Biochemistry results were within normal limits except moderate elevations in alkaline phosphatase, lactic dehydrogenase, and β_2-microglobulin levels. In May 1997, splenectomy was performed. Histologic examination of the spleen showed atrophy of the germinal centers, with partial destructions of the white pulp. The red pulp seemed expanded with its sinusoids homogenously infiltrated with lymphoid cells, which were positive for LCA and CD3. A similar infiltration pattern was observed in the hepatic sinusoids.

After splenectomy, the liver enlarged to the umbilicus. The pancytopenia improved (Hb 11.7 g/dl, Hct 34.7%, platelets 256×10^9/l, neutrophils 4×10^9/l) but the peripheral blood smear showed atypical lymphoid cells varying between 35% and 45%. A second bone marrow biopsy three months after splenectomy showed an infiltration with the same neoplastic cells in a diffuse interstitial pattern. In the immunophenotyping of peripheral blood after splenectomy with flow cytometry, the ratio of the γδ T-cell receptor (TCR) bearing lymphoid cells was 59%. CD2, CD3, CD5, CD7, and CD56 positivity ranged between 70 and 99%. The heteroduplex analysis of peripheral blood showed that this pattern carried the monoclonal TCR Vγ-1 gene (Fig. 1).

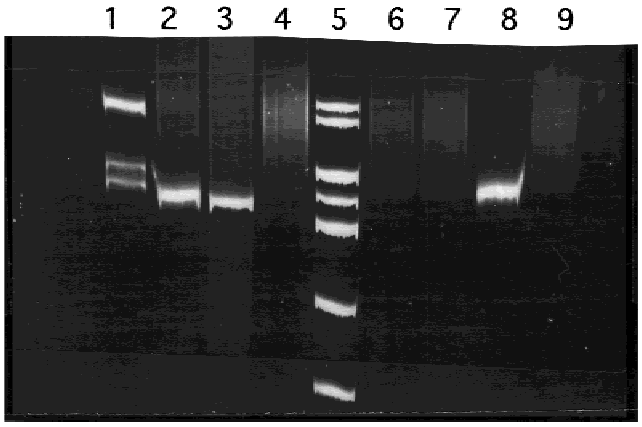

Fig. 1. Polyacrylamide gel electrophoresis with TCR Vγ1 and Vγ2 primers after PCR amplification. (PCR with TCR Vγ1 and Vγ2 primers were for lanes 1 to 4 and 6 to 9, respectively. Lanes 1 and 6: case A; lanes 2 and 7: our patient; lanes 3 and 8: positive control; lanes 4 and 9: typical polyclonal smear sample from normal lymphocytes; lane 5: Marker-BM no. VIII)

The patient did not respond to chemotherapy. Neither regimens with conventional doses (CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone) nor that with high doses of methotrexate and/or cytosine arabinoside (NHL-BFM-90) proved to be effective. In May 1998 his condition deteriorated progressively and he died 13 months after diagnosis.

The presence of pancytopenia with severe neutropenia at presentation, seems to be an uncommon manifestation as it has been observed in only three of the 23 patients with hepatosplenic γδ TCL reported in the medical literature until the time of this writing [3,4]. Thus, the patient presented seems to be the fourth case displaying this feature. Another important finding in this case was the presence of hypersplenism due to the infiltration of the red pulp of the spleen in a manner resembling that seen in hairy cell leukemia. Splenectomy has, similarly, corrected this hypersplenism only by increasing the number of peripheral blood cells [5] without any effect on the disease process, progression being evident by the appearance of abnormal lymphoid cells in the peripheral blood. Thus, despite high-dose chemotherapy, the course of the disease was concluded as progressive in this case due to the persistence of B symptoms, increased hepatomegaly, and peripheral blood involvement. It can also be concluded that hypersplenism may also account for the cytopenias besides bone marrow infiltration and that splenectomy, like chemotherapy, seems ineffective in altering the progressive course of the disease.

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Günçağ Dinçol
Meliha Nalçaci
A. Selim Yavuz
Hüseyin Keskin
Melih Aktan
Division of Hematology, Istanbul Medical School, Istanbul, Turkey

Öner Doğan
Mehmet Ağan
Division of Pathology, Istanbul Medical School, Istanbul, Turkey
Uğur Özbek
Institute for Experimental Medicine, University of Istanbul, Istanbul, Turkey
Koray Dinçol
Institute of Oncology, University of Istanbul, Çapa, Istanbul, Turkey

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